THE ASSOCIATION BETWEEN LUMBAR PUNCTURE AND THE SUBSEQUENT DEVELOPMENT OF BACTERIAL MENINGITIS IN CHILDREN WITH UNSUSPECTED BACTEREMIA

Nelson Harris Aaron

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A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

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Nelson Harris Aaron

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ABSTRACT

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THE SUBSEQUENT DEVELOPMENT OF BACTERIAL MENINGITIS
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Over the past 100 years there has been much controversy over whether or not lumbar puncture performed in an unsuspectedly bacteremic child could predispose the child to the later development of bacterial meningitis. In this thesis the medical records of 186 children with unsuspected bactermia in New Haven were reviewed; there was no association found between lumbar puncture and subsequent development of bacterial meningitis when the children were stratified by the identity of the causative organism of the bacteremia and the clinical presentation of the child at the time of the initial visit . Furthermore, the identity of the causative organism of bacteremia was very strongly associated with the subsequent development of bacterial meningitis. Thus it is concluded that the performance of a lumbar puncture does not predispose children with unsuspected bacteremia to the subsequent development of bacterial meningitis.

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Chapter I

INTRODUCTION

There is a controversy concerning the association between the performance of a lumbar puncture and the subsequent development of bacterial meningitis in children with unsuspected bacteremia. There have been published several studies on animals and children both supporting and attacking this hypothesis. The purpose of this thesis is to present a retrospective clinical study of cases of unsuspected bacteremia in children that have occurred at Yale-New Haven Hospital in recent years and examine the association between lumbar puncture and the subsequent development of bacterial meningitis while controlling for the effect of other important clinical variables.

Bacterial meningitis is a relatively "recent" disease. The first description of meningitis was made by Vieusseux in 1805 Geneva. He described an epidemic of meningitis associated with a rash of "purple spots."[1] Before the late nineteenth century, bacterial meningitis, early in its course, was difficult to distinguish from aseptic meningitis. However, the perfection of the technique of lumbar puncture by Heinrich Quincke[2] made possible the rapid and accurate diagnosis of bacterial meningitis[3].

At first the lumbar puncture was felt to be an extremely benign procedure[4]. However, by the early 20th century there were scattered reports of cases of bacterial meningitis developing within a few days following a normal spinal tap, as in this case described by Wegeforth:

> This soldier (Pvt. T.) was being treated for pneumonia, and early in the morning of October 23 the emergency night officer was called to administer to him for a headache. The officer detected what he thought to be the rash of a meningococcus septicemia on the patient's chest and sent for the ward surgeon on the meningitis service for consultation. This surgeon examined the man at 5:30 a.m. and found no evidence of meningitis or meningococcus infection, the rash having turned out to be typical acne. In order to be sure and satisfy himself, as well as the surgeon in charge of the case, of the correctness of the diagnosis, he made a lumbar puncture. The fluid obtained was perfectly clear, contained but two cells per c.mm. and no red cells. As a matter of routine (for no one suspected the patient of having a septicemia) a specimen of blood was taken for culture, which revealed the presence of a pneumococcus (type 1) infection. On the following evening (October 24) the patient began to show unmistakable signs of irritation within the central nervous system and a second spinal fluid withdrawn at this time (thirty six hours after the first) gave positive evidence of meningitis, the infecting organism being the pneumococcus (type 1). Intraspinal therapy with the specific antipneumococcus serum was immediately instituted without effect and the patient died on the morning of October 25. Autopsy showed a typical pneumococcus leptomeningitis, with secondary hydrocephalus[5].

As a result of these reports, there was much interest in the scientific community to determine if lumbar puncture predisposes a bacteremic patient to developing bacterial meningitis. These studies demonstrated a relationship between lumbar puncture and the development of meningitis in bacteremic laboratory animals[6]. However, evidence of meningitis developing after lumbar puncture in bacteremic humans consists only of several anecdotal reports and several conflicting studies[7].

Whether a lumbar puncture predisposes a child with unsuspected bacteremia to the subsequent development of bacterial meningitis is of great importance to the practicing Pediatrician. At present there are no certain means of identifying children who are bacteremic from those who simply have a viral illness without associated bacteremia[8]. Furthermore, in children who are known or suspected to be bacteremic the

problem of meningitis induced by a lumbar puncture is moot, as the initial antimicrobial therapy for these children would effectively treat meningitis.

The most common pathogen in children with unsuspected bacteremia is the pneumococcus[9]. However, *H. influenzae* type b is the most common pathogen isolated from the cerebrospinal fluid of children with bacterial meningitis[10]. This implies that the different bacteria may have different predelictions for invading the central nervous system. Thus, since the risk of developing meningitis may vary with the identity of the organism, unless this is controlled for in a study on the the relationship between lumbar puncture and bacterial meningitis, conclusions about the effect of lumbar puncture may be erroneous.

To examine this problem, a retrospective study of children with unsuspected bacteremia at Yale New-Haven Hospital was undertaken to determine if a lumbar puncture at the time of initial evaluation was associated with the deveolpment of bacterial meningitis. Furthermore, information was obtained about other factors that might be independently associated with both lumbar puncture at the time of the initial visit and the subsequent development of bacterial meningitis, such as the clinical appearance of the child at the time of the initial evaluation, so that the effect of the lumbar puncture could be assessed while controlling for the effects of other possibly confounding factors.

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Chapter II

HISTORICAL REVIEW

2.1 A SURVEY OF EXPERIMENTAL WORK ON LABORATORY ANIMALS

By the late nineteenth century there was much research on the pathogenesis of bacterial meningitis using laboratory animals. Netter[1] had postulated a hematogenous route of infection for bacterial meningitis when he observed meningitis occurring in dogs which had had pneumococci injected into their lungs. A second possible route of infection was thought to be direct extension via the nasal passages through the sphenoid sinus, as many patients were observed to develop meningitis as a complication of mastoiditis or sinusitis[2].

Flexner[3] first showed that direct innoculation of the subarachnoid space with bacteria caused meningitis. He innoculated rhesus monkeys with intrathecal pneumococci of various types and reported the development of pneumococcal meningitis in these animals after two or three days. A similar experiment using meningococci in guinea pigs was performed later by Branham[4].

After World War I, investigators became concerned over whether spinal trauma could predispose a bacteremic patient to the development of bacterial meningitis. Austrian[5] studied the development of meningococcal meningitis in rabbits given a lumbar puncture followed by an intravenous or intranasal innoculation of meningococci. He found that rabbits given an intranasal bolus of meningococci did not develop meningitis regard-

less of whether or not they had received a lumbar puncture; also, rabbits given intravenous meningococci alone did not develop meningitis. However, of 20 rabbits given an intravenous bolus of meningococci 20 minutes after receiving 2 cc of intrathecal rabbit serum, 5 developed meningococcal meningitis. He concluded that cerebrospinal fluid is infected hematogenously, not by direct extension via the sphenoid sinus, and postulated that hyperemia of cerebral vessels secondary to spinal trauma in the presence of bacteremia predisposes animals to bacterial meningitis. Amoss[6] performed similar experiments using rhesus monkeys and reached the same conclusions. However, it should be noted that lumbar puncture in rabbits causes bleeding into the cerebrospinal fluid and meningitis in these animals could have resulted from direct invasion of the cerebrospinal fluid by bacteria in the blood[7].

At the same time, Weed[8] was interested in whether the withdrawal of cerebrospinal fluid would predispose septicemic cats to developing bacterial meningitis. Control animals given an intravenous dose of *B. mucosus capsulatum* without receiving a lumbar puncture did not develop meningitis, whereas animals given an intravenous bolus of bacteria followed by a lumbar puncture did develop meningitis. It was noted that the dose of bacteria needed to induce meningitis varied directly with the interval between the intravenous bolus and the lumbar puncture, and that meningitis could not be induced if the lumbar puncture and intravenous bolus were performed more than thirty minutes apart. Weed[9] next observed meningitis after cerebral congestion in cats made septicemic with *B. mucosus capsulatum;* cerebral congestion was induced by jugular compression or by intravenous hypertonic saline. Lumbar puncture with

replacement of withdrawn cerebrospinal fluid or lumbar puncture without withdrawal of cerebrospinal fluid protected cats from developing meningitis only if the lumbar puncture was performed before the cat was made bacteremic. Finally, some cats were sacrificed at various intervals after the lumbar puncture to observe the pathologic course of meningitis. Invariably the meningeal exudate formed around the brain and was not found at the site of lumbar puncture. From these observations Weed concluded that lumbar puncture does predispose bacteremic animals to bacterial meningitis, and that the pathogenesis of infection involved the physiologic lowering of the blood brain barrier by lumbar puncture and the withdrawal of cerebrospinal fluid.

There are some pitfalls involved in reaching this conclusion, though. First, the maneuvers performed by Weed to produce cerebral congestion are known to cause diffuse hemorrhagic encephalopathy in cats[10], thus the bacteria may have gained access to the cerebrospinal fluid by a mechanical break in the blood brain barrier. Second, Weed was unable to demonstrate exactly where the lumbar puncture site was, thus making a pathologic examination of the site difficult[11]. Third, with respect to withdrawal and replacement of removed cerebrospinal fluid, Weed never measured cerebrospinal fluid pressure. Thus a quantitative relation between cerebrospinal fluid hemodynamics and the subsequent development of bacterial meningitis never was demonstrated. Finally, *B. mucosus capsulatum* is not a normal human pathogen, thus it is difficult to compare the pathogenicity of this bacterium in cats with the pathogenicity of a human pathogen, e.g. *H. influenzae* type b, in humans.

Two more early animal studies are worthy of note. Idzumi[12] compared the development of pneumococcal meningitis in rabbits and dogs. He found that intravenous injection of pneumococci alone lead to meningitis, but intravenous pneumococci followed by subthecal saline lead to the development of pneumococcal meningitis in some rabbits but not in dogs. Finally, subthecal injection of pneumococci invariably resulted in meningitis in rabbits but only occasionally resulted in meningitis in dogs. He concluded that a lumbar puncture may predispose a bacteremic patient to develop meningitis but noted that there are considerable differences between in the results obtained with different animal species. Remson[13] performed similar experiments on rabbits and found that on pathologic examination some of the animals developed a spinal exudate, concluding that it may be possible to produce meningitis by the mechanical introduction of bacteria into the subarachnoid space in a bacteremic patient given a lumbar puncture.

Harter[14], in a literature review, stated a number of problems with the early studies on laboratory animals. He noted a lack of uniform organisms and host animals, and a general lack of quantification of laboratory results (eg. cerebrospinal fluid pressures, incidence of meningitis in laboratory animals receiving a lumbar puncture) in most of the previously named studies. An ideal situation was proposed for animal studies on this topic:

(1) The portal of entry and route of dissemination of bacteria should be similar to that in man.

(2) The parasite should be pathogenic to man.

(3) The course of disease should be predictable.

(4) Lesions produced should be morphologically similar to those found in man.

(5) The technique employed in producing the lesions should be simple[15].

Petersdorf[16] undertook a study of experimental pneumococcal meningitis in dogs. Control animals who received intravenous pneumococci without a cisternal puncture did not develop meningitis. Experimental animals recieved a varying dose of intravenous pneumococci followed by a cisternal puncture two minutes later in which 2 cc of cerebrospinal fluid was removed. Cerebrospinal fluid cultures, white blood cell counts, glucose, pressures, and quantitative blood cultures were measured at the time of cisternal puncture and later as needed. The incidence of subsequent bacterial meningitis varied with the dose of pneumococci in a step-wise fashion: if the dose of pneumococci contained fewer than 10^3 bacteria the dogs did not develop meningitis; if the dose contained more than 10^3 bacteria there was a uniform dose-independent incidence rate of 50-75%. Since there was some scatter in the incidence rate and since different dogs may have cleared bacteria at different rates, the relationship between the level of bacteremia in the animals and the development of meningitis was studied. There was a direct relationship between the number of organisms in the bloodstream and the subsequent development of pneumococcal meningitis.

Petersdorf[17] next studied the mode of spread of infection in the central nervous system. There were greater numbers of organisms found in the cerebrospinal fluid than in the meningies or brain tissue suggesting that bacteria entered the cerebrospinal fluid directly from the

bloodstream rather than passing through the meninges first. Also, there were no pathologic or clinical differences between pneumococcal meningitis caused by direct intrathecal innoculation versus cisternal puncture in bacteremic animals, suggesting that the mode of infection was similar for both.

Finally, changes in cerebrospinal fuild pressure and blood brain barier permeability were studied. No cases of meningitis in bacteremic animals occurred after intravenous dextran infusion (lowering cerebrospinal fluid pressure 50%), jugular venous occlusion (elevating cerebrospinal fluid pressure 50%), or intravenous typhoid vaccine innoculation (increasing blood brain barrier permeability). Intrathecal normal saline (producing aseptic meningitis) followed by intravenous pneumococci did not result in pneumococcal meningitis. There was no correlation between opening pressure, closing pressure, or change in cerebrospinal fluid pressure and the subsequent development of bacerial meningitis in dogs[18].

Petersdorf[19] concluded that it is possible to induce pneumococcal meningitis in bacteremic dogs with a cisternal puncture, with the incidence of post-cisternal puncture pneumococcal meningitis increasing with increasing concentrations of bacteria in the blood. Furthermore, the pathogenesis of this infection was by direct invasion of the cerebrospinal fluid at the site of cisternal puncture and not by indirect alterations of either the hemodynamics of the cerebrospinal fluid or the characteristics of the blood brain barrier.

The applicability of these studies to humans is unclear. The levels of bacteremia needed to produce meningitis that were achieved by Peters-

dorf are several orders of magnitude higher than those routinely seen in infants and children with pneumococcemia[20]. Furthermore, Petersdorf studied the pneumococcus only. A handful of researchers[21] studied meningococcal meningitis, however, there are no animal studies of *H. influenzae* type b meningitis and its relation to lumbar puncture. On the other hand, Petersdorf used dogs, in which meningitis is more difficult to produce experimentally than in other animals[22].

Thus, there have been many experimental studies using laboratory animals in the past century which attempt to prove a link between lumbar puncture and the subsequent develpoment of bacterial meningitis. However, it is difficult to induce bacterial meningitis in laboratory animals; a level of bacteremia much higher than what is usually seen in humans had to be attained in order to produce meningitis in laboratory animals. Furthermore, the bacteria studied in the most detail in animal experiments, *S. pneumoniae,* is not the most common pathogen associated with bacterial meningitis in children; *H. influenzae* type b and *N. meningitidis,* which are responsible for most cases of bacterial meningitis in children have not been investigated in the same detail. Thus, the results of the animal studies are of limited value in determining if lumbar puncture predisposes an unsuspectedly bacteremic child to subsequently developing bacterial meningitis.

2.2 A SURVEY OF CLINICAL STUDIES

Before embarking on this survey, it should be noted that all clinical studies on the possible role of lumbar puncture in the pathogenesis of bacterial meningitis in children are flawed. The closest approximation to an ideal study of this problem would entail a prospective study of a large number of children who present with fever but without bacterial meningitis or other immediate life threatening illness (ie. acute epiglottitis). They would be randomly assigned to either receive a lumbar puncture or not receive a lumbar puncture. Complete blood counts (including differential white blood counts) and quantitative blood cultures would be taken of all children and the children would be admitted to the hospital and observed without antibiotics for a few days or until they developed bacterial meningitis. Daily complete blood counts, quantitative blood cultures and lumbar punctures would be performed on all children. From this pool, those children who were initially bacteremic could be selected and the relative risk of developing meningitis after a lumbar puncture could be accurately assessed by organism and clinical status of the child. Needless to say, this study in which children would be randomly assigned to receive an invasive procedure and denied treatment is too unethical to be considered as a method to solve the problem at hand. However, even this study is flawed, as it would be impossible to determine if the children who did not receive a lumbar puncture at initial examination had meningitis at that time.

There are scattered anecdotal reports of cases of meningitis occuring after lumbar puncture in bacteremic patients, both appearing as isolated cases[23] and as incidental findings in studies reviewing cases of unsu-

spected bacteremia[24]. These reports certainly raise the question of whether or not lumbar puncture predisposes a bacteremic child to the subsequent development of bacterial meningitis, but provide no answers.

Wegeforth[25] prospectively studied 93 patients who received a lumbar puncture between September, 1917 and November, 1918. Thirty eight of the 93 had documented bacterial meningitis on initial lumbar puncture and were excluded. Of the 55 remaining patients 49 had a negative blood culture at the time of lumbar puncture, none developed bacterial meningitis subsequently. There were six patients whose blood culture was positive but who did not initially have meningitis. Three patients had pneumococcemia, two of whom subsequently developed pneumococcal meningitis. Three patients had meningococcemia, all of whom subsequently developed meningococcal meningitis. Wegeforth concluded that lumbar puncture may be a predisposing factor in the subsequent development of bacterial meningitis in bacteremic subjects. Two points should be made about this study. First, Wegeforth did not include any cases of *H. influenzae* type b meningitis - which is not surprising since *H. influenzae* type b was not discovered until eight years after this study was published. Second, he did not compare the cases presented to those cases of bacteremia who did not receive a lumbar puncture as part of their diagnostic evaluation, thus his study was not controlled.

Pray[26] published a large survey of infants and children with pneumococcal meningitis, pneumonia, and pneumococcemia at Babies' Hospital, Johns Hopkins Hospital, Grace-New Haven Hospital, New York Hospital, and Boston Children's Hospital. He found that in 6% of 207 cases of pneumococcal meningitis the patient had received a lumbar puncture before the

TABLE 1

Relationship Between Lumbar Puncture and Meningitis (Pray, 1941).

Patients < 2 years old:

	Meningitis	No Meningitis	
Lumbar Puncture	7	14	
No Lumbar Puncture	70	163	P > 0.1

Patients > 2 years old:

	Meningitis	No Meningitis	
Lumbar Puncture	1	16	
No Lumbar Puncture	8	137	P > 0.1

development of meningitis, and that 80% of the 207 cases occured in children less than two years of age. He concluded that lumbar puncture preceeds meningitis in a relatively small number of cases and that infants and toddlers are at a higher risk for developing pneumococcal meningitis than are other children.

Pray[27] next studied cases of meningitis complicating pneumonia. He found that bacterial meningitis was a very uncommon complication of pneumonia, occurring in 102 of 11,742 cases of pneumonia. In a study of 321 cases of pneumonia at Babies Hospital, 33 (10%) developed signs of meningismus; 19 had a lumbar puncture as part of their diagnostic evaluation and none developed bacterial meningitis. However, all 19 cases had sterile blood cultures at the time of lumbar puncture.

Finally, Pray[28] reviewed 416 cases of pneumococcemia. He found that there was no significant difference in the incidence of pneumococcal meningitis in patients who received a lumbar puncture while bacteremic and those who did not (table 1). He concluded that lumbar puncture

does not predispose a bacteremic child to developing bacterial meningitis, and suggests that lumbar puncture should be performed where necessary, since "...to make a diagnosis of meningitis is frequently impossible on the basis of symptoms and physical signs alone."[29]

Dripps[30] studied complications of spinal anesthesia. In a retrospective study of 8,460 patients given 10,098 spinal anesthetics between 1948 and 1951 he could find no cases of bacterial meningitis following spinal anesthesia. The results were based on answers to a questionnaire given to patients and there is no note of the number of bacteremic patients (probably very rare) receiving spinal anesthesia, however it can be concluded that meningitis following spinal anesthesia is a rare event, although cases have been documented[31].

Myers[32] reported seven cases of children with unsuspected pneumococcemia, all of whom received a lumbar puncture as part of their initial evaluation. Three of the seven subsequently developed pneumococcal meningitis within four days of the lumbar puncture. Likewise, Fischer[33] reported four cases of children with bacterial meningitis following a lumbar puncture with normal results. It should be noted that one of the children cited in Fischer's study had a sterile blood culture at the time of the initial lumbar puncture. Neither investigator assessed the outcomes of bacteremic children who did not receive a lumbar puncture as part of their initial workup.

Bratton[34] reviewed 97 episodes of unsuspected pneumococcemia between September, 1971 and November, 1975. He found four cases of meningitis arising as a complication of unsuspected pneumococcemia. Of the four cases, three cases were preceeded by lumbar puncture at initial

evaluation. There were 17 children who had a lumbar puncture at initial evaluation. Bratton concluded that it is possible that lumbar puncture is associated with subsequent development of bacterial meningitis in bacteremic children. However, he never compared the clinical status of the children who received lumbar punctures to those who did not. Bacteremic children who have a higher concentration of bacteria in their bloodstream may appear to be more ill and be more likely to receive a lumbar puncture. Therefore, if meningitis as a complication of bacteremia is dependent on the concentration of bacteria in the bloodstream, then the children in Bratton's study could have developed meningitis because they had a higher level of bacteremia with the lumbar puncture being an incidental procedure done on initial examination[35].

Eng[36] reviewed 1,089 cases of bacteremia, 200 of whom had received a lumbar puncture. Of these 200, 30 had had bacterial meningitis at the time of initial assessment. Only three of the remaining 170 cases subsequently developed bacterial meningitis. Eng concluded that lumbar puncture does not predispose bacteremic patients to developing bacterial meningitis. However, he did not compare his group to a group which did not receive lumbar punctures, nor did he stratify his group based on clinical presentation or type of bacteria found in the blood. Most cases of bacteremia are due to *S. pneumoniae,* but *N. meningitidis* and *H. influenzae* type b are the most common bacteria found in cases of bacterial meningitis[37]. Therefore, if the frequency with which lumbar puncture is performed is different in patients with pneumococcemia than in patients with meningococcemia or *H. influenzae* type b bacteremia, the subsequent development of bacterial meningitis may appear to be due to

the performance of the lumbar puncture, when it actually is secondary to the type of bacteria present in the blood.

Teele[38] reported the results of a retrospective study of children with unsuspected bacteremia between 1971 and 1980 at Boston City Hospital. Children who had meningitis (and other focal infections) at the time of initial evaluation as well as any others who were admitted and treated with intravenous antibiotics were excluded from the study. Children were considered to have bacterial meningitis if the cerebrospinal fluid had a culture that was positive for the same pathogen found in the blood or the presence in the cerebrospinal fluid of at least eight white blood cells and/or more than one polymorphonuclear cell (PMN) with normal glucose, protein, sterile spinal fluid culture and positive blood culture.

There were 277 children with unsuspected bacteremia: 212 with pneumococcemia, 56 with *H. influenzae* type b bacteremia, and 8 with meningococcemia. Of these patients, 79% were under 2 years of age, 91% had a temperature at the time of initial visit that was greater than 38.9 degrees, and 75% had a peripheral white blood count that was greater than 15,000. There were 137 children who did not receive antibiotic therapy and 140 children who received either intramuscular or oral antibiotics. The median time to follow-up was two days. There were 46 patients who received a lumbar puncture on initial visit. There were 9 cases of bacterial meningitis on follow-up, 7 of which occurred in children who had received a lumbar puncture at their prior visit, as shown in table 2. It is interesting to note that no cases of follow-up meningitis occurred in children older than one year. Teele claimed no significant differ-

TABLE 2

Association Between Menigitis and Prior Lumbar Puncture (by age). (Teele, 1981)

	Untreated		Treated		
Age < 1 year:	LP	No LP	LP	No LP	
Meningitis at f/u	5	1	2	1	
No Meningitis	1	41	15	54	
					P=0.003
Age > 1 year:	LP	No LP	LP	No LP	
Meningitis at f/u	0	0	0	0	
No Meningitis	15	74	8	60	
					Not Sig.

ence between those patients who developed meningitis and those who did not in sex, race, initial temperature, presence of seizures, organism in blood culture, white blood count, or differential white blood count[39].

On the basis of these data, Teele[40] concluded that the significant association between lumbar puncture and the subsequent development of bacterial meningitis might be explained by one or more of the following hypotheses:

(1) Lumbar puncture may lead to the development of meningitis in certain children - those under one year of age who have not received antibiotic therapy after having the lumbar puncture.

(2) Clinical judgement may enable the physician to select the child in whom meningitis is developing before the spinal fluid is diagnostic.

(3) Meningitis may not be present at the initial evaluation, but bacteremia may be more advanced in children who receive lumbar puncture[41].

There are several problems with Teele's study which have not been adequately addressed in the paper. First, he did not stratify the groups which did and did not receive lumbar punctures by clinical presentation, organism causing the bacteremia, initial diagnosis, or time until follow-up. For example, 8% of the patients with pneumococcemia received lumbar punctures but 30% of the patients with *H. influenzae* type b bacteremia had a lumbar puncture[42]. Also, of the patients with these organisms and meningitis at follow-up, 6/8 (75%) had disease due to *H. influenzae* type b. Thus since there was a higher rate of lumbar puncture the relatively small number of children with *H. influenzae* type b bacteremia (which more commonly causes bacterial meningitis, as was described earlier) as compared to the larger group of children with pneumococal bacteremia, the association found between lumbar puncture and the subsequent development of bacterial meningitis may actually be due simply to the greater predeliction of *H. influenzae* type b for invading the cerebrospinal fluid.

Another problem arises in the broad criteria Teele used to establish the diagnosis of bacterial meningitis in cases of equivocal lumbar puncture results, as in these three cases which were diagnosed as bacterial meningitis by Teele: (1) An 11 month old female who had a lumbar puncture revealing cerebrospinal fluid with 200 white cells, 25% PMN's and a sterile spinal fluid culture without having received antibiotic therapy for two days following a lumbar puncture, (2) A 10 month old female who had a follow-up lumbar puncture with a sterile spinal fluid culture four days after intial lumbar puncture without having received antibiotic therapy, (3) A 10 month old female who returned after nine days of oral

amoxicillin and had a lumbar puncture which had 63 white blood cells with 5% PMN's and sterile blood and spinal fluid cultures[43]. Using a broad definition of bacterial meningitis in a study of this type (thus calling cases of viral meningitis or "sympathetic meningitis" bacterial meningitis) may cause performance of a lumbar puncture to be falsely significantly associated with the subsequent development of bacterial meningitis, as the number of cases of lumbar puncture on initial visit who went on to develop bacterial meningitis at follow-up may be increased relative to the number of cases without meningitis on follow-up and relative to the number of cases of meningitis at follow-up who did not receive a lunbar puncture at initial visit.

Finally, Teele reports that lumbar puncture is significantly associated in the subsequent development of bacterial meningitis in children less than one year of age. However, there is no reason why infants should be more susceptible to the development of meningitis after a lumbar puncture than their older siblings. However, if younger children have a higher incidence of *H. influenzae* type b infections than older children, and if there is a difference in the frequency of lumbar puncture for bacteremias caused by different organisms, the association between lumbar puncture and the subsequent development of bacterial meningitis in this age group could be explained on the basis of the different types of bacteria having different predelictions for infecting the central nervous system.

Thus, although Teele presents some evidence that lumbar puncture may be associated with the subsequent development of bacterial meningitis in children with unsuspected bacteremia, his argument is weakened since he

did not investigate the possible roles that the clinical status of the patient, initial diagnosis, and identity of organism of bacteremia play in receiving a lumbar puncture and developing bacterial meningitis. This study is designed to examine the possible association between lumbar puncture and the subsequent development of bacterial meningitis in children with unsuspected bacteremia while controlling for potentially confounding variables, such as the clinical status of the patient and the type of organism causing the bacteremia.

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Chapter III

THE ASSOCIATION BETWEEN LUMBAR PUNCTURE AND THE SUBSEQUENT DEVELOPMENT OF BACTERIAL MENINGITIS IN CHILDREN WITH UNSUSPECTED BACTEREMIA.

3.1 METHODS

A list of all pediatric patients with bacteremia due to *Streptococcus pneumoniae, Haemophilus influenzae* type b, or *Neisseria meningitidis* was obtained from the pediatric blood culture log at Yale-New Haven Hospital between January 1, 1971 and July 1, 1983. The medical records of all patients were reviewed and all data pertinent to their initial and follow-up presentations were extracted. If no mention was made in the medical records for a historical symptom, physical sign, of laboratory result, then data for that finding was recorded as "not mentioned" or "not done." For the purposes of the study, a "positive history" at the time of the initial visit was defined as one in which there was one or more of the following complaints: a history of lethargy and/or irritability, or a history of seizures. A "positive physical examination" was defined as one or more of the following findings: an irritable, lethargic or "toxic" appearing child, the presence of nuchal rigidity with or without a positive Kernig's or Brudzinski's sign, or the presence of a full or bulging anterior fontanelle.

For children not taking antibiotics at the time of or soon before their presentation, meningitis was defined as a positive cerebrospinal fluid culture for either *H. influenzae* type b, *S. pneumoniae,* or *N. men-*

ingitidis. For those patients who were receiveing antibiotics at the time of or soon before their presentation, bacterial meningitis was defined either as a positive cerebrospinal fluid culture for one of the organims listed above, or a cerebrospinal fluid pleocytosis of at least 100 white blood cells of any type with greater than 50% polymorphonuclear cells. A list of cases of bacterial meningitis on follow-up visit is provided in appendix B.

All children admitted to the hospital and treated with intravenous antibiotics were excluded from the study. Also, all children whose medical records contained no record of any follow-up after the initial visit were excluded from the study. Data were analyzed using SAS on an IBM 4341 computer.

3.2 RESULTS

3.2.1 Clinical Features of Patients with Unsuspected Bacteremia.

Between Janaury 1, 1971 and July 1, 1983, 544 patients less than 16 years of age had a blood culture positive for either *S. pneumoniae, H. influenzae* type b, or *N. meningitidis* at Yale-New Haven Hospital. Of these, 336 patients were excluded because they received intravenous antibiotic therapy at initial visit, and 22 patients were excluded because there was no follow-up recorded in the chart (111 cases of *S. pneumoniae* bacteremia, 231 cases of *H. influenzae* type b bacteremia, and 16 cases of *N. meningitidis* bacteremia). The 186 patients remaining had what will be referred to as unsuspected bacteremia -- 139 cases of unsuspected pneumococemia, 40 cases of unsuspected *H. influenzae* type b

TABLE 3

Patients with Unsuspected Bacteremia at Yale-New Haven Hospital Between January, 1971 and July, 1983.

Total cases of unsuspected bacteremia		186
Mean age (mo.)		25.1
Sex: Male		96
Female		90
Time of blood culture:	1/1971-12/1973:	13
	1/74-12/76:	64
	1/77-12/79:	36
	1/80-6/83:	73
Blood culture:		
	S. pneumoniae	139
	H. influenzae type b	40
	N. meningitidis	7

bacteremia, and 7 cases of unsuspected meningococcemia. The clinical features of these patients are summarized in tables 3 to 5. The only statistically significant differences in the initial presenting clinical features of patients with pneumococcal, meningoccal, or *H. influenzae* type b bacteremia were in their mean temperature, history of poor feeding, white blood count, and treatment after initial visit. The clinical features of these children stratified by the organism causing the bacteremia are summarized in appendix C.

TABLE 4

Clinical Features of Patients with Unsuspected Bacteremia at the Time of Initial Presentation.

1) Median Duration of Symptoms (days)		2	
2) History of	- Temp. > 38.5 C (1)	74	(183)
	- Irritability and/or lethargy	127	(152)
	- Decreased feeding	89	(132)
	- Stiff neck	2	(12)
	- Seizures	15	(24)
3) Physical Examination:			
	- Mean temp.(Cent.)	39.72	(180)
	- Appearance not normal	121	(176)
	- Neck stiff	6	(157)
	- Ant. fontanelle full	3	(51)
4) Laboratory Studies:			
	- Mean WBC	17770	(181)
	- Mean %PMN's	55.8	(171)
	- Mean %Bands	15.8	(171)
	- Mean ESR	28.4	(106)
5) Lumbar Puncture Done		58	(186)
6) Diagnosis:	- Fever / Viral Syndrome	63	
	- Otitis Media	59	
	- Pneumonia	22	
	- O.M. + Pneumonia	6	
	- Aseptic Meningitis	2	
	- R/O Sepsis	9	
	- Other	21	
	- Not noted	4	
7) Antibiotic Treatment:			
	- None	84	
	- Oral pen/amp/amox.	82	
	- i.m. pen/amp	4	
	- i.m. + p.o. pen/amp	9	
	- other i.m. + p.o.	7	

Note (1): Numbers in parentheses represent the total number of patients in which data about the presence or absence of the sign or symptom was present in the medical records.

TABLE 5

Clinical Features of Patients with Unsuspected Bacteremia at the Time of Follow-up.

1) Median Time to Follow-up (days)	2	
2) Interim History:		
- Temp. > 38.5 C (1)	28	(178)
- Irritability and/or lethargy	75	(172)
- Decreased feeding	49	(144)
- Stiff Neck	5	(31)
- Seizures	3	(29)
3) Physical Examination:		
- Mean temp.(Cent.)	38.0	(174)
- Appearance not normal	66	(177)
- Neck stiff	14	(148)
- Ant. font. full/bulging	9	(55)
4) Laboratory Studies:		
- Mean WBC	14630	(132)
- Mean %PMN's	46.2	(124)
- Mean %Bands	8.5	(124)
- Mean ESR	40.6	(74)
5) Lumbar Puncture Done	72	(186)
6) Blood culture same as initial culture	35	(137)
7) Diagnosis: - Fever / Viral Syndrome	4	
- Otitis Media	35	
- Pneumonia	27	
- O.M. + Pneumonia	7	
- Transient Bacteremia	56	
- Persistent Bacteremia	5	
- Bacterial Sepsis	20	
- Aseptic Meningitis	3	
- Bacterial Meningitis	12	
- Other	17	
8) Antibiotic Treatment:		
- None	31	
- Oral pen/amp/amox.	56	
- i.m. + p.o. pen/amp	2	
- i.v. antibiotics	96	

Note (1): Numbers in parentheses represent the total number of patients in which data about the presence or absence of the sign or symptom was present in the medical records.

3.2.2 Clinical Presentation of Children with Unsuspected Bacteremia Who Recieved a Lumbar Puncture at the Initial Visit.

In this section the relation between the clinical presentation of the child and the performance of a lumbar puncture will be investigated. In table 6 the clinical presentation of children with unsuspected bacteremia who did and did not receive a lumbar puncture at initial assessment is presented, and in table 7 the laboratory data of children with unsuspected bacteremia who did and did not recieve a lumbar puncture is presented. As can be seen in the tables, age, mean temperature, mean white blood cell count, a "positive" history and physical examination are significantly associated with the performance of a lumbar puncture. Although there were statistically significant differences in the means of white blood count and temperature of patients who did and did not receive a lumbar puncture, when these continuous variables were analyzed as categorical variables as a clinician might (for example patients with temperature greater than 39.5 C), the differences in the categorical groups were not statistically significant. It is also of note that there is a significant association between the organism causing the bacteremia and the performance of a lumbar puncture, with a disproportionately low number of cases of *H. influenzae* type b bacteremia having received a lumbar puncture.

TABLE 6

Clinical Presentation of Children with Unsuspected Bacteremia at Initial Visit Based on the Performance of a Lumbar Puncture.

	Lumbar Puncture		No Lumbar Puncture		Prob.(1)
Total Cases	58		128		
Mean Age (mo.) (2)	14.4	(58)	29.9	(128)	P=0.001
Median Age (mo.)	13		15		
Age < 12 months	26	(58)	39	(128)	P=0.05
HISTORY:					
Median Duration of Symptoms (days)	2		2		NS
Irritable/lethargic	46	(53)	81	(99)	NS
Decreased feeding	26	(43)	59	(89)	NS
Stiff Neck	2	(5)	0	(7)	NS
Seizure	12	(16)	3	(8)	NS
"+ History"	47	(58)	82	(128)	P=0.02
PHYSICAL EXAM:					
Mean Temp (C)	39.96	(56)	39.62	(124)	P=0.011
Temp. > 39.0 C	48	(56)	101	(124)	NS
Temp. > 39.5 C	45	(56)	83	(124)	NS
Temp. > 40.0 C	35	(56)	63	(124)	NS
Irritable/lethargic/toxic	43	(58)	78	(118)	NS
Neck Stiff	5	(55)	1	(102)	P=0.041
Ant. Font. Full	2	(27)	1	(24)	NS
"+ Physical Exam"	13	(58)	10	(128)	P=0.005

Notes:
(1) Probabilities for categorical variables were determined by chi square analysis; probabilities for continuous variables were determined using the Student's t test; NS= not significant.
(2) Numbers in parentheses represent the total number of cases in which there is explicit information about the factor contained in the medical records.

TABLE 7

Laboratory Data of Children with Unsuspected Bacteremia at Initial Visit Based on the Performance of a Lumbar Puncture.

	Lumbar Puncture	No Lumbar Puncture	Prob.(1)
Total Cases	58	128	
LABORATORY DATA:			
Mean WBC	19090 (57)	17160 (124)	P<0.05
WBC > 15000	44 (57)	85 (124)	NS
Mean %PMN's	52.9 (53)	57.0 (118)	NS
Mean %Bands	16.9 (53)	15.3 (118)	NS
Mean ESR	27.2 (28)	28.9 (78)	NS
BLOOD CULTURE:			
S. pneumoniae	46	93	
H. influenzae type b	7	33	
N. meningitidis	5	2	P=0.011

Notes:
(1) Probabilities for categorical variables were determined by chi square analysis; probabilities for continuous variables were determined using the Student's t test; NS= not significant.
(2) Numbers in parentheses represent the total number of cases in which there is explicit information about the factor contained in the medical records.

3.2.3 The Association Between the Clinical Presentation of Children with Unsuspected Bacteremia at Initial Assessment and the Subsequent Development of Bacterial Meningitis.

In the previous section it was demonstrated that there were significant differences in the clinical presentation of children with unsuspected bacteremia who received a lumbar puncture compared with those who did not receive a lumbar puncture at the time of the initial assessment. If the clinical presentation of children with unsuspected bactermia is associated with the subsequent development of bacterial meningitis, then the association between lumbar puncture and the subsequent

TABLE 8

The Association Between the Clinical Presentation of Children with Unsuspected Bacteremia and the Subsequent Development of Bacterial Meningitis.

	Meningitis	No Meningitis	Prob.(1)
Total cases	12	174	
Mean age (mo.) (2)	20.5 (12)	25.4 (174)	NS
Median age (mo.)	17	16	
Age < 12 months	5 (12)	60 (174)	NS
"+ History"	9 (12)	120 (174)	NS
"+ Physical Exam"	4 (12)	19 (174)	P=0.0451
Mean temp. (Cent)	40.15 (12)	39.69 (168)	P=0.0657
Mean WBC	13720 (12)	18060 (169)	P=0.0267
WBC > 15000	5 (12)	124 (169)	P=0.0500
Mean %PMN's	54.8 (12)	55.8 (159)	NS
Mean %Bands	20.9 (12)	15.4 (159)	NS
Mean ESR	24.2 (6)	28.7 (100)	NS
Antibiotic Rx after initial visit	3 (12)	99 (174)	P=0.0640
Median interval between visits	1 (12)	2 (174)	NS

Notes:
(1) Probabilities for categorical variables were determined by Fisher's Exact Test; probabilities for continuous variables were determined using Student's t test; NS= not significant (P>0.05)
(2) Numbers in parentheses represent the total number of cases in which data pertinent to the finding is contained in the medical records.

development of bacterial meningitis may be incidental to the association between the "degree of illness" of the patient and the subsequent development of bacterial meningitis. In table 8 the association between the clincal features at the time of presentation of the patient and the subsequent development of bacterial meningitis is summarized. As can be seen in the table, a "positive" physical examination, and mean white blood count at initial assessment are significantly associated with the

TABLE 9

The Association Between Lumbar Puncture and the Subsequent Development of Bacterial Meningitis in Children with Unsuspected Bacteremia.

	Subsequent Meningitis	No Subsequent Meningitis	Total
Lumbar Puncture	7 (58%)	51 (29%)	58 (31%)
No Lumbar Puncture	5 (42%)	123 (71%)	128 (69%)
Total	12 (100%)	174 (100%)	186 (100%)

Odds Ratio= 3.38, 95% Confidence limits: 1.08 to 10.55
Chi Square= 4.41, $P<0.05$

subsequent development of bacterial meningitis. Furthermore, mean temperature and antibiotic therapy at intial assessment are almost significantly associated with the subsequent development of bacterial meningitis.

3.2.4 Association Between Lumbar Puncture and the Subsequent Development of Bacterial Meningitis.

The association between lumbar puncture and the subsequent development of bacterial meningitis is summarized in table 9. There is a statistically significant association between lumbar puncture and the subsequent development of bacterial meningitis in children with unsuspected bacteremia. The odds ratio between lumbar puncture and the subsequent development of bacterial meningitis shows that those children with bacterial meningitis were three and one half times more likely to have received a lumbar puncture on initial examination as those children with unsuspected bacteremia who did not develop bacterial meningitis.

TABLE 10

The Association Between the Organism Causing Bacteremia and the Subsequent Development of Bacterial Meningitis.

	Meningitis	No Meningitis	Total
S. pneumoniae	3 (25%)	136 (78%)	139
H. influenzae type b	5 (42%)	35 (20%)	40
N. meningitidis	4 (33%)	3 (2%)	7
Total	12 (100%)	174 (100%)	186

Chi Square= 36.473, P<0.0001

3.2.5 The Relation Between the Causative Organism of Bacteremia and the Subsequent Development of Bacterial Meningitis.

Of the 186 children with unsuspected bacteremia, 139 (74.7%) had unsuspected pneumococcemia, however, of the 12 children who developed bacterial meningitis subsequent to the initial evaluation, only 3 (25%) had pneumococcal meningitis. The association between the identity of the organism found in the blood culture and the subsequent development of bacterial meningitis is shown above in table 10. As can be seen , there is a very significant association between the organism causing bacteremia and the subsequent development of bacterial meningitis. Children with unsuspected bacteremia due to *H. influenzae* type b or *N. meningitidis* were much more likely to develop bacterial meningitis than children with unsuspected pneumococcemia.

Next, the association between lumbar puncture and the subsequent development of bacterial meningitis in children with unsuspected bacteremia while controlling for the identity of the organism causing the bac-

TABLE 11

The Association Between Lumbar Puncture and the Subsequent Development of Bacterial Meningitis in Children with Unsuspected Bacteremia Stratified by the Organism Causing the Bacteremia.

S. pneumoniae	Meningitis	No Meningitis	Total
Lumbar Puncture	2	44	46
No Lumbar Puncture	1	92	93
Total	3	136	139

H. influenzae type b	Meningitis	No Meningitis	Total
Lumbar Puncture	2	5	7
No Lumbar Puncture	3	30	33
Total	5	35	40

N. meningitidis	Meningitis	No Meningitis	Total
Lumbar Puncture	3	2	5
No Lumbar Puncture	1	1	2
Total	4	3	7

Mantel-Haenszel Test:
Mantel-Haenszel chi=1.739
Chi square for heterogeneity=0.527
Mantel-Haenszel odds ratio=3.416, P=0.0818
95% confidence limits: (0.855, 13.63)

teremia was investigated. The results are shown above in table 11. As can be seen by the results of the Mantel-Haenszel analysis of the data, lumbar puncture is not significantly associated with the subsequent development of bacterial meningitis when the patient population is stratified by the identity of the causative organism of the bacteremia. However, although with stratification by the organism causing the

bacteremia the p-value rose to 0.08, the odds ratio was virtually unchanged. Thus, the effect of stratification by blood culture on the association between lumbar puncture and the subsequent development of bacterial meningitis is negligible, with the lack of significance of the association probably due to the sample size of cases of unsuspected bacteremia being too small.

Stratification by blood culture alone does not take into account the effects of the other possible confounding variables. In previous sections it was shown that children who received lumbar punctures had different ages, temperatures, histories, physical examination findings, and white blood counts at the time of the initial visit than those who did not receive a lumbar puncture, and children who subsequently developed bacterial meningitis had different ages, temperatures, histories, physical examination findings, white blood counts, and were treated differently at the time of the initial visit than those bacteremic children who did not develop meningitis subsequently. Thus, these variables, since they are unevenly distributed between children who received lumbar punctures and those who did not and are also unevenly distributed between children who did and did not subsequently develop bacterial meningitis, can be confounding variables of the association between lumbar puncture and the subsequent development of bacterial meningitis. Thus, since stratification by a single variable does not take into account the effect of other variables, a logistic regression model was created in the next section to examine the effect of all the possible confounding variables on the association between lumbar puncture and the subsequent development of bacterial meningitis in children with unsuspected bacteremia.

3.2.6 A Multivariate Analysis of the Association Between Lumbar Puncture and the Subsequent Development of Bacterial Meningitis in Children with Unsuspected Bacteremia.

In previous sections, it was shown that the age, temperature, white blood count, physical examination, identity of the causative organism of bacteremia, and antibiotic therapy at the time of the initial visit was associated with both receiving a lumbar puncture and subsequently developing bacterial meningitis. Therefore, these clinical features relevant to the decision made at the time of the initial visit to perform a lumbar puncture and associated with the subsequent development of bacterial meningitis may confound the association between lumbar puncture and the subsequent development of bacterial meningitis. In this section a multivariate model of the subsequent development of bacterial meningitis will be created in order to investigate how controlling for the effects of these possible confounding variables affects the magnitude of the association between lumbar puncture and the subsequent development of bacterial meningitis.

A model for the data from this study was created using the logistic regression procedure in SAS described by Harrell[1]. The logistic regression procedure enables the investigator to examine the magnitude of the efect that an independent variable has on the dependent variable while controlling for the effects of other independent variables. The logistic regression creates a regession parameter, beta, for each independent variable in the model. The odds ratio for each independent variable is the natural antilogarithim of beta.

In all models of the data used in this thesis, the only dependent variable is the subsequent development of bacterial meningitis. For

TABLE 12

Logistic Regression Model for the Association Between Lumbar Puncture and the Subsequent Development of Bacterial Meningitis.

Dependent Variable: Subsequent bacterial meningitis.
Independent Variable: Lumbar puncture at initial visit.

	Odds Ratio	95% Conf. Limits	Sig.(1)
Lumbar Puncture	3.38	(1.02,11.13)	0.046

Note: (1) The significance is a measure of the probability that the odds ratio is equal to one.

models in which data for the causative organism of bacteremia is used, cases of pneumococcal bacteremia are used as a standard against which cases of *H. influenzae* type b and *N. meningitidis* bacteremias are compared. The results for the odds ratios for the causative organisms of bacteremia and the subsequent development are presented as two variables, "*H. influenzae*" and "*N. meningitidis,*" in which an odds ratio of "R" for the former variable means that in the model patients with *H. influenzae* type b bacteremia are "R" times as likely to develop bacterial meningitis subsequently as are patients with pneumococcemia, and an odds ratio of "S" for the latter variable means that patients with meningococcemia are "S" times as likely to develop bacterial meningitis as are patients with pneumococcemia. The significance value is a measure of the probability that the odds ratio is equal to one.

First, a model for the data in which only lumbar puncture at the time of initial presentation is used as an independent variable. The results are shown in table 12. The odds ratio for lumbar puncture in this model is similar to the odds ratio derived in the 2x2 contingency table for lumbar puncture and the subsequent development of bacterial meningitis

TABLE 13

The Effect of Controlling for the Clinical Presentation on the Association Between Lumbar Puncture and the Subsequent Development of Bacterial Meningitis.

Variable Added to Model in Table 12	Odds Ratio of Lumbar Puncture	Percent Change in Odds Ratio of Lumbar Puncture
None added	3.38	
Age	3.34	-1.18%
"+ History"	3.34	-1.18%
"+ Phys. Exam"	2.76	-18.3%
Temperature	2.69	-20.5%
WBC>15000	4.17	+23.5%
Antibiotic Rx	2.92	-13.5%
Blood Cx Result	3.41	+1.07%

Notes: (1) The variable "Blood Cx Result" is the composite effect of comparing patients with meningococcemia or *H. influenzae* type b bacteremia with patients with pneumococcemia.
(2) Odds ratios shown are for lumbar puncture and the subsequent development of bacterial meningitis.

shown earlier. Once again it should be remarked that the odds ratio for lumbar puncture and the subsequent developoment of bacterial meningitis is just barely significant because the variance of the odds ratio is high.

Next, a separate logisitic regression model of the data, using both lumbar puncture and each one of the possible confounding variables individually as independent variables, was created to see what effect each of the possible confounding variables had on the odds ratio for lumbar puncture. The results, in table 13, are presented as the odds ratio for lumbar puncture in the model in which lumbar puncture and the clinical variable were used as independent variables, and the change in the odds

ratio represents the change in the odds ratio for lumbar puncture from the original model (table 12). It was found that inclusion into the model of each of the possible confounding variables, except white blood count, caused the odds ratio for lumbar puncture and the subsequent development of bacterial meningitis to decrease. Temperature, a "positive physical examination," and antibiotic therapy after initial visit when used as independent variables each resulted in odds ratios for lumbar puncture that were much lower than when lumbar puncture was considered as the sole independent variable.

Finally, a model for the subsequent development of bacterial meningitis using all of the independent variables discussed above is presented in table 14. The adjusted odds ratio for lumbar puncture in this model is much lower than the odds ratio for lumbar puncture when it is considered alone -- a change from 3.38 to 1.099 (67% decrease). Since the odds ratio for lumbar puncture in this model is virtually equal to one, the association between lumbar puncture and the subsequent development of bacterial meningitis while controlling for the causative organism of bacteremia and the clinical presentation of the child at the time of the initial visit is very weak. The highest odds ratios found in the model were those comparing children with *H. influenzae* type b and *N. meningitidis* bacteremia to children with pneumococcal bacteremia. Children with meningococcemia were found to be 80 times as likely and children with *H. influenzae* type b bacteremia were found to be 11 times as likely to subsequently develop bacterial meningitis as were children with pneumococcemia, when controlling for the effects of the other variables.

TABLE 14

A Multivariate Model for the Subsequent Development of Bacterial Meningitis Using All Clinical and Laboratory Data.

Dependent Variable: Subsequent bacterial meningitis

Independent Variables:
- -Lumbar Puncture
- -Age
- -Specific organism in blood Cx (2)
- -History at initial visit
- -Physical Exam at initial visit
- -Antibiotic therapy after initial visit
- -WBC > 15000
- -Temperature at initial visit

Variable	Odds Ratio	95% Conf. Limits	Sig.(1)
Lumbar Puncture	1.099	(0.181,6.659)	NS
Age	0.991	(0.948,1.055)	NS
H. influenzae	11.08	(2.036,60.25)	0.0054
N. meningitidis	80.31	(4.596,1403.1)	0.0027
"+ History"	0.996	(0.113,8.812)	NS
"+ Phys."	3.909	(0.732,20.88)	NS
Antibiotics	0.306	(0.057,1.649)	NS
WBC >15000	0.520	(0.115,1.649)	NS
Temperature	3.316	(1.105,10.83)	0.0471

Notes: (1) Significance is a test of the null hypothesis that the odds ratio equals one. NS= not significant (P>0.05)

(2) The variable *H. influenzae* represents the comparison between chidren with *H. influenzae* type b and pneumococcal bacteremia. The variable *N. meningitidis* represents the comparison between children with meningococcemia and pneumococcemia.

Also, the odds ratios comparing children with the different causative organisms of bacteremia were the only odds ratios significantly different than one (except for temperature). Thus, the identity of the causative organism of bacteremia is the variable most strongly associated with the subsequent development of bacterial meningitis.

The odds ratios for the clinical variables "positive physical examination", temperature, white blood count, and antibiotic therapy at the time of the initial presentation were all very different than one (as compared with the odds ratio for age and "positive history" which were virtually equal to one), but only the odds ratio for the temperature was significantly different than one. However, the lack of significance of the other odds ratios may be due to a lack of statistical power in the model, eg. if there were a greater number of cases of unsuspected bacteremia to begin with these odds ratios may become significant. It is also interesting to note that the odds ratio for patients with white blood counts greater than 15,000 is less than one; patients with higher white blood counts tended to subsequently develop bacterial meningitis less often than children with lower white blood counts. Finally, there were no significant interaction effects between lumbar puncture and any of the other independent variables in the model.

3.3 DISCUSSION

The data presented show that in children with unsuspected bacteremia the odds ratio for the association between lumbar puncture at the time of the initial evaluation and the subsequent development of bacterial meningitis is 3.4 and is statistically significant. When this estimate is adjusted for possible confounding variables, such as the type of organism causing the bacteremia and the clinical presentation of the patient at the time of initial visit, the odds ratio approaches unity. In other words, when the clinical state of the patient at the time of the initial visit is taken into account, unsuspectedly bacteremic children

who subsequently developed bacterial meningitis are no more likely to have received a lumbar puncture at the time of initial presentation than those bacteremic children who did not subsequently develop bacterial meningitis. In particular, the odds ratio for lumbar puncture and the subsequent development of bacterial meningitis was substantially lowered by each of the following: the presence of a "positive" physical examination (an irritable, lethargic, or "toxic" appearing child, and/or the presence of nuchal rigidity, and/or the presence of a full or bulging anterior fontanelle) at the time of initial presentation, temperature at the time of initial presentation, or the administration of antibiotic therapy after the initial presentation. It is also interesting that the age of the patient did not independently change the odds ratio for lumbar puncture and the subsequent development of bacterial meningitis.

Of even greater importance was the finding that the identity of the causative organism of bacteremia was the factor most strongly associated with the subsequent development of bacterial meningitis. Controlling for the effect of other potential confounding variables including having undergone a lumbar puncture at the time of the initial visit, the subsequent development of bacterial meningitis was six times as likely to have developed in children with unsuspected *H. influenzae* type b bacteremia than pneumococcal bacteremia, and sixty times as likely to have developed in patients with unsuspected meningococcemia than in those with pneumococcemia. This effect of the organism on the likelihood of subsequently developing bacterial meningitis was unchanged even after controlling for the effects of other potentially confounding variables, such as the temperature and white blood count at the time of the intial

visit. It can be concluded that the identity of the the organism causing the bacteremia is associated with the subsequent development of bacterial meningitis independent of the clinical presentation of these children at the time of initial visit; this confirms that the different bacteria have different propensities for invading the central nervous system.

The results of this study differ in some respects from the results from the study by Teele[2]. First, Teele used a broader definition of bacterial meningitis than used in this study. If the use of this definition would cause the number of cases of children who had received a lumbar puncture and subsequently developed bacterial meningitis to increase out of proportion to the increase in the total number of cases of bacterial meningitis which developed subsequent to the initial visit, then the use of this definition could bias the association between lumbar puncture and the subsequent development of bacterial meningitis in children with unsuspected bacteremia. Second, it is interesting that Teele found no cases of bacterial meningitis arising in children with unsuspected bacteremia who were older than one year, whereas in this study there were 7 cases of bacterial meningitis on follow-up occuring in this age group. As was stated in chapter 2, there is no logical reason why bacteremic children over one year of age should be "protected" from the subsequent development of bacterial meningitis. The only possible explanation for this would be if there was an age difference between children who had unsuspected bacteremia due to *S. pneumoniae* and *H. influenzae* type b, however, this hypothesis is not supported by the results of this study, in which there was no significant difference in the

ages of children with *S. pneumoniae*, *H. influenzae*, or *N. meningitidis* bacteremia. Also, there was a surprising difference between Teele's study and this study in the proportion of children who had received a lumbar puncture when stratified by the type of bacteremia. Teele found that 30% of the children with *H. influenzae* type b bacteremia had received a lumbar puncture and 8% of the children with unsuspected pneumococcemia had received a lumbar puncture[3], whereas in this study, at the time of initial visit, 7/40 (18%) of the children with unsuspected *H. influenzae* type b bacteremia received a lumbar puncture and 46/139 (33%) of the children with unsuspected pneumococcemia received a lumbar puncture. It is possible that the difference between the studies in the percent of children with *H. influenzae* type b bacteremia who received a lumbar puncture is due to chance ($p>0.05$ by chi-square); however, it is very unlikely that the difference between the studies in the percent of children with pneumococcemia who received a lumbar puncture is due to chance ($p<0.0001$ by chi-square). If it is assumed that children in Boston are similar to children in New Haven it is difficult to explain these differences. Perhaps, if in Teele's study, there was an age difference in the children who had bacteremia due to *S. pneumoniae* and *H. influenzae* type b, this could explain the difference between Teele's study and this study, since younger children are more likely to receive a lumbar puncture than older children (as was shown in table 6). However, there was no significant difference in age between children with unsuspected *H. influenzae* type b and *S. pneumoniae* bacteremia in this study, thus this theory is not supported by the data of this study.

The results of this thesis offer a possible reconciliation of the conflicting results of Teele's study[4] and Pray's earlier study[5]. Teele found a significant association between lumbar puncture and the subsequent development of bacterial meningitis in children with unsuspected bacteremia. Pray, in a study of children with pneumococcemia found that there was no association between lumbar puncture and the subsequent development of bacterial meningitis. In this thesis there was a significant association between lumbar puncture and the subsequent development of bacterial meningitis in children with unsuspected bacteremia, but only when no other clinical features of these patients were considered. However, when the patients were stratified by the organism causing the bacteremia the association between lumbar puncture and the subsequent development of bacterial meningitis is not significant. Thus, could have been possible for Teele to find a significant association between lumbar puncture and the subsequent development of bacterial meningitis in children with unsuspected bacteremia and Pray to find no association between lumbar puncture and the subsequent development of bacterial meningitis in children with pneumococcemia.

Next, the results from this study suggest that the concentration of bacteria in the blood may be associated with the subsequent development of bacterial meningitis in children with unsuspected bacteremia. In the multivariate model developed in the results, the odds ratio for a "positive physical examination" (a physical examination in which the child was noted to be irritable, lethargic, or "toxic", or in which the child was noted to have a nuchal rigidity or a full or bulging anterior fontanelle) at the time of the initial visit and the subsequent development

of bacterial meningitis was much greater than one when controlling for the effects of all the other possible confounding variables (including the presence of a lumbar puncture at the time of the initial visit and the identity of the causative organism of bacteremia), meaning that children with unsuspected bacteremia who presented at the time of the initial visit with the physical findings listed above were at a greater risk for the subsequent development of bacterial meningitis. The odds ratio for temperature at the time of the initial visit and the subsequent development of bacterial meningitis was significantly different from one when the effects of all other possible confounding variables are considered. A possible explanantion for these findings is that children who have a higher concentration of bacteria in the blood may appear to be more ill (thus being more likely to present with a higher temperature and a physical examination which is positive for the findings listed above) at the initial presentation and be more likely to subsequently develop bacterial meningitis, independent of the identity of the causative organism of bacteremia and the performance of a lumbar puncture at the time of the initial presentation.

For the white blood count, the odds ratio of children with unsuspected bacteremia who presented with a white blood count less than 15,000 and the subsequent development of bacterial meningitis was greater than one, however, the difference in white blood counts for children with unsuspected bacteremia who did and did not subsequently develop bacterial meningitis was not great. The white blood count may be slightly lower in children with a high concentration of bacteria in the blood on the basis of a more rapid turnover of polymorphonuclear cells. There was an

odds ratio greater than one for children who did not receive antibiotic therapy after the initial visit and the subsequent development of bacterial meningitis when the effects of all other possible confounding variables was considered, implying that the administration of antibiotic therapy after the initial visit is somehow proctective against the subsequent development of bacterial meningitis. Oral (or a single dose of intramuscular) antibiotic therapy after the initial presentation, while perhaps not sufficient to clear the bacteremia entirely, may decrease the concentration of bacteria enough to decrease the risk of subsequently developing bacterial meningitis. Therefore, the results of this study provide evidence that the concentration of bacteria in the blood may be associated with the subsequent development of bacterial meningitis; however, since quantitative blood cultures were not measured in the children in this study, conclusions about the association between the concentration of bacteria in the blood and the subsequent development of bacterial meningitis can be made by inference only.

Because only the records of children with unsuspected bacteremia and not the records of all children who presented with fever were studied, the findings of associations between certain aspects of the clinical presentation of the children at the time of the initial visit and the subsequent development of bacterial meningitis are not applicable to deciding if the child who presents with fever is at risk for the subsequent development of bactrerial meningitis. The use of countercurrent immunoelectrophoresis or latex agglutination could identify some children with *H. influenzae* type b, *S. pneumoniae,* or *N. meningitidis* bacteremia at the time of initial visit, in which case, the results found

in this thesis could be helpful in determining if they are at risk for the subsequent development of bacterial meningitis. However, currently latex agglutination is not a very specific test, and CIE is not very sensitive, thus many children who are bacteremic will have negative CIE's and many children who are not bacteremic will have positive latex agglutination tests. Therefore, latex agglutination and CIE are of limited usefulness in determining which children are at risk for the subsequent development of bacterial meningitis. Thus, the identification of children who have unsuspected bacteremia and are at risk for the subsequent development of bacterial meningitis remains an unsolved problem.

The results of this study suggest that there is no significant risk of inducing bacterial meningitis in children with unsuspected bacteremia by performance of a lumbar puncture. However, some of the problems inherent in retrospective studies in general and some difficulties specific to a study of lumbar puncture and the subsequent development of bacterial meningitis limit the conclusions that can be drawn from this thesis:

(1) Because children without bacteremia were not included in the study, all the associations between the clinical presentation at initial visit and the subsequent development of bacterial meningitis are of very little value, as it is not known at the time of initial presentation if the child is bacteremic.

(2) All children did not receive an ESR at the time of the initial visit. If it assumed that the more "ill appearing" children are more likely to have a high ESR, and are more likely to receive an ESR at the time of the initial presentation, then since it was shown that

children who had a "positive physical examination" and a higher temperature at the time of the initial visit were at a greater risk for the subsequent development of bacterial meningitis, then it could follow that the mean ESR of children who did not subsequently develop bacterial meningitis was factitiously high, thus reducing the difference in mean ESR between children who did and did not subsequently develop bacterial meningitis.

(3) Since there are no data for the concentration of bacteria in the bloodstream all conclusions about the effect of the concentration of bacteria in the blood and the subsequent development of bacterial meningitis are speculative.

(4) The race of a child with unsuspected bacteremia may be associated with the subsequent development of bacterial meningitis, or it may be a confounding variable in the association between the causative organism of the bacteremia and the subsequent development of bacterial meningitis.

(5) The administration of antibiotic therapy after the initial visit was shown to have an odds ratio with the subsequent development of bacterial meningitis that was less than one when the possible contribution of all the other variables was considered. However, the appropriateness of the type of antibiotic therapy to the organism causing the bacteremia was not considered -- there were nine cases of *H. influenzae* type b bacteremia in which penicillin was administered after the initial visit. Bacterial meningitis did not subsequently develop in any of the nine, nor did any of the nine present at the time of follow-up with *H. influenzae* type b bacteremia.

These cases were considered to have had antibiotic therapy after the initial visit in this study (as the bacteremia cleared in all of the cases). However, if these cases are not considered as having received "appropriate" antibiotic therapy then the odds ratio for antibiotic therapy after the initial visit and the subsequent development of bacterial meningitis would be closer to one.

(6) It is difficult to establish criteria for cerebrospinal fluid findings which can distinguich all cases of bacterial and nonbacterial meningitis, particularly when "early" cases of bacterial meningitis or "partially treated" cases of bacterial meningitis are considered (a brief review of the controversies in the criteria for the diagnosis of bacterial meningitis is provided in appendix A).

As was described in Chapter 2, a randomized clinical study of children who are febrile in the clinic or emergency room examining the association between lumbar puncture and the subsequent development of bacterial meningitis in children with unsuspected bacteremia would be impossible to do. However, a prospective study of all febrile children who present in the emergency room or clinic to examine the association between lumbar puncture and the subsequent development of bacterial meningitis could be arranged which would solve the problems of this study that are listed above.

There are several reasons why a clinician should not be deterred from performing a lumbar puncture on a febrile child suspected of having bacterial meningitis. First, there is the need to know immediately if the child has bacterial meningitis and there currently are no better means known to diagnose bacterial meningitis. Second, the occurrence of bac-

terial meningitis after a lumbar puncture is uncommon among children with unsuspected bacteremia (only 7 cases in the last 12 years at Yale-New Haven Hospital). Finally our results suggest that the apparent association between lumbar puncture and the subsequent development of bacterial meningitis disappears after adjustment for differences in the causative organism of bacteremia and the clinical presentation of the child. Therefore, the clinician should not hesitate from performing a lumbar puncture when it is deemed to be a necessary part of the diagnostic evaluation of a febrile child.

[1] Harrell, SAS Supplemental Library User's Guide, 1980 Ed., 1980, pp.83-84.

[2] Teele *et al.*, N. Eng. J. Med., 1981.

[3] B. Dashefsky, personal communication.

[4] Teele *et al.*, N. Eng. J. Med., 1981.

[5] Pray, Am. J. Dis. Child., 1941.

Chapter IV

CONCLUSIONS

(1) Lumbar puncture, when considered alone, is significantly associated with the subsequent development of bacterial meningitis in children with unsuspected bacteremia, however, when the children are stratified based on the clinical presentation at the time of the initial visit and by the organism causing the bactermia, lumbar puncture is no longer associated with the subsequent development of bacterial meningitis.

(2) The identity of the organism causing the bacteremia is the factor most strongly associated with the subsequent development of bacterial meningitis in children with unsuspected bacteremia.

Appendix A

CONTROVERSIES IN THE DIAGNOSIS OF ACUTE BACTERIAL MENINGITIS

One of the major concerns in this thesis has been just what differentiates bacterial from aseptic (or no) meningitis on lumbar puncture findings. Teele[1] used a very broad definition of bacterial meningitis in his study (see chapter 2 section 2) and was criticized for it[2]. Unfortunately, in attempting to differentiate bacterial and viral meningitis the results of cell counts and chemistries of the cerebrospinal fluid may not be diagnostic[3]. This is complicated by the possible effect of oral antimicrobial therapy on the reliability of cerebrospinal fluid cultures, especially in "early" or equivocal cases of meningitis[4].

In 1899, Osler[5] described the classic signs and symptoms of patients with bacterial meningitis - abrupt onset of high variable fever with shaking chills, rash, arthralgias and periarteritis, lethargy progressing to obtundation, stiff neck, positive Kernig's sign, leukocytosis of blood and cerebrospinal fluid, etc. Later, Smith[6] described differing presentations for children of varying ages, noting that neonates are more likely to present with cyanosis, fever, and vomiting, whereas children over the age of two most often present with fever, lethargy, and headache. Carpenter[7] described the different presentating symptoms of pneumococcal, meningococcal, and *H. influenzae* type b meningitis. It is of note that there are some differences in presenting history among cau-

sative organism, but for this discussion it is more important to note that the only historical finding found in most patients was fever. Carpenter also found that stiff neck was not seen in 19% of the cases reviewed. Thus it is very difficult to make a diagnosis of bacterial meningitis on history and physical exam alone, and a lumbar puncture should be done whenever there is reasonable suspicion that the patient has bacterial meningitis[8].

The results of a single lumbar puncture unfortunately cannot often differentiate between bacterial and viral meningitis. Carpenter[9] reported a large degree of overlap between viral and bacterial meningitis, especially pneumococcal meningitis. Wheeler[10], in an editorial, echoed this and stated the need to retap questionable cases. Feigin[11] reviewed 590 patients with meningitis and found 37 patients who had aseptic meningitis with initial lumbar puncture findings suggestive of bacterial meningitis and 48 patients with bacterial meningitis whose intial lumbar puncture was suggestive of aseptic meningitis. Milne[12], in a review of the literature states two reasons why bacterial and aseptic meningitis are difficult to differentiate:

(1) The variability of CSF white counts in cases of bacterial meningitis, as low as one to twenty,

(2) The increased cellularity of CSF in normal infancy.

There are several anecdotal reports of cases of meningitis in which some lumbar puncture findings did not match the final diagnosis. Moore[13] reported three cases of bacterial meningitis with positive cerebrospinal fluid cultures and otherwise normal cerebrospinal fluid. Milne reported two similar cases[14]. On the other hand, Frazier[15]

reported two cases of cerebrospinal fluid pleocytosis without meningitis but with concommitant bacterial infection, which he called "sympathetic meningitis." Musher[16] reported four cases of false positive cerebrospinal fluid gram stain (contaminated samples) confusing diagnosis and treatment of the cases.

The conclusion that all the researchers drew is that a single lumbar puncture in and of itself cannot be used to differentiate bacterial and viral meningitis. They all suggest repeat lumbar puncture within 24 hours of an equivocal tap to aid in eventual diagnosis and treatment[17]. Shinefield[18] adds that repeat lumbar puncture shoud be performed in cases where the first tap was equivocal only if the clinical condition of the patient necessitates it.

Another difficulty in differentiating bacterial and viral meningitis arises when the child has received antibiotic therapy before having a lumbar puncture with equivocal results. Quaade[19], in an retrospective study of 658 cases of purulent meningitis in Copenhagen found that a significant proportion (35%) of the patients had received some form of antibiotic therapy before receiving the lumbar puncture. Harter[20] studied 70 patients with meningitis, 34 of whom had received antibiotics before the lumbar puncture. He could find no significant difference in cerebrospinal fluid white count, glucose, or protein between the treated and untreated groups. Dalton[21] reviewed 310 cases of bacterial meningitis, 158 who received antibiotics before lumbar puncture. The only significant differences between the treated and untreated groups were in cerebrospinal fluid culture (88% of untreated group positive vs. 59% of treated group), gram stain (53% of untreated group positive vs. 35% of

treated group), and blood culture (23.4% of untreated group positive vs. 8.5% of treated group). Similar results were found in a later study by Jarvis[22]. Winkelstein[23], in a chart review of cases of meningitis could find no difference in presenting history or physical exam findings between children with bacterial meningitis who had and had not received oral antibiotics before lumbar puncture.

Converse[24] studied children with meningitis who were or were not treated before admission. He found that the laboratory values for the children in the treated group who had sterile cultures was similar to those who had aseptic meningitis in the untreaed group. He concluded that there may be a small group of patients with bacterial meningitis in whom antibiotic therapy may have altered cerebrospinal fluid laboratory values. However, it is assumed that treated children with sterile cerebrospinal fluid cultures have bacterial meningitis. Feldman[25] studied 93 pediatric patients admitted to the hospital for treatment of bacterial meningitis, and found that the concentrations of *H. influenzae* type b and *N. meningitidis* in cerebrospinal fluid were significantly lower in patients who had received oral antibiotic therapy before lumbar puncture than those who had not. However, the concentration of *S. pneumoniae* in the spinal fluid of these two groups pf patients was not siginificantly different. Lastly, Blazer[26] reviewed the records of 68 children with previously untreated bacterial meningitis. The results of the admission lumbar puncture were compared with results of a follow-up lumbar puncture done 44 to 68 hours later. He could find no significant changes in cerebrospinal fluid characteristics except that the culture became sterile after 44 hours. He concluded that if high dose antibiotic therapy

does not change the characteristics of cerebrospinal fluid, then partial treatment should not either.

The major criticism of the preceeding set of studies is that most if not all of the children who were observed had fulminant meningitis, with high white counts and a high percentage of polymorphonuclear cells in the cerebrospinal fluid. However, children with early meningitis or children who had equivocal results of lumbar punctures were not studied in sufficient numbers. Thus, the results of the preceeding studies do not completely answer the question of whether prior partial antibiotic therapy alters the characteristics of children with early meningitis.

Therefore, there is a dilemma in how to proceed with cases whose lumbar puncture findings are equivocal - those patients with cerebrospinal fluid pleocytosis and a positive blood culture but sterile cerebrospinal fluid culture and those patients who had been treated with oral antibiotics who have cerebrospinal fluid pleocytosis but sterile cerebrospinal fluid and blood cultures. Teele[27] defined all the equivocal cases as bacterial meningitis. However, by doing so he may be biasing his data by including cases of aseptic and "sympathetic" meningitis with actual cases of bacterial meningitis. Thus, the proportion of children with bacterial meningitis at the time of the follow-up visit may be artificially high as compared with the children who did not receive a lumbar puncture at the time of the initial visit. On the other hand to call all equivocal cases non-bacterial meningitis risks underestimating the number of cases of bacterial meningitis in the group and thus biasing the data in the opposite direction. However, since most of the findings in the literature suggest that only the culture and gram stain results

are altered by prior antibiotic therapy, in this study bacterial meningitis was defined as a positive cerebrospinal fluid culture for either *H. influenzae* type b, *S. pneumoniae*, or *N. meningitidis* or a cerebrospinal fluid pleocytosis of greater than 100 total white blood cells with at least 50% polymorphonuclear cells with a sterile cerebrospinal fluid culture for children who had been treated with antibiotic before the lumbar puncture -- a definition narrower than used by Teele[28].

[1] Teele *et al.*, N. Eng. J. Med., 1981.

[2] Teele *et al.*, N. Eng. J. Med., 1982.

[3] Carpenter *et al.*, Am. J. Med., 1962; Wheeler, J. Pediatr., 1970; Milne *et al.*, N.Z. Med. J., 1976; Moore *et al.*, Clin. Pediatr., 1973; Musher *et al.*, Ann. Intern. Med., 1973; Frazier *et al.*, Clin. Pediatr., 1981; Rapkin, Pediatr., 1974; Blazer *et al.*, Am. J. Clin. Path., 1983.

[4] Quaade *et al.*, Acta. Med. Scand., 1962; Harter, Arch. Neurol., 1963; Dalton *et al.*, Am. J. Clin. Path., 1968; Winkelstein, J. Pediatr., 1970; Jarvis *et al.*, Clin. Pediatr., 1972; Converse *et al.*, J. Pediatr., 1973; Feldman, Am. J. Dis. Child. 1978; Blazer *et al.*, Am. J. Clin. Pathol., 1983.

[5] Osler, Brit. Med. J., 1899.

[6] Smith, Pediatr., 1956.

[7] Carpenter *et al.*, Am. J. Med., 1962.

[8] *ibid.*; Pray, Am. J. Dis. Child., 1941.

[9] Carpenter *et al.*, Am J. Med., 1962.

[10] Wheeler, J. Pediatr., 1970.

[11] Feigin *et al.*, N. Eng. J. Med., 1973.

[12] Milne *et al.*, N.Z. Med. J., 1976.

[13] Moore *et al.*, Clin. Pediatr., 1973.

[14] Milne *et al.*, N.Z. Med. J., 1976.

[15] Frazier *et al.*, Clin. Pediatr., 1981.

[16] Musher *et al.*, Ann. Intern. Med., 1973.

[17] Feigin *et al.*, N. Eng. J. Med., 1973; Rapkin, Pediatr., 1974; Milne *et al.*, N.Z. Med. J., 1976; Frazier *et al.*, Clin. Pediatr., 1981.

[18] Shinefield, Am. J. Dis. Child., 1975.

[19] Quaade *et al.*, Acta. Med. Scand., 1962.

[20] Harter, Arch. Neurol., 1963.

[21] Dalton *et al.*, Am. J. Clin. Path., 1968.

[22] Jarvis *et al.*, Clin. Pediatr., 1972.

[23] Winkelstein, J. Pediatr., 1970.

[24] Converse *et al.*, J. Pediatr., 1973.

[25] Feldman, Am. J. Dis. Child., 1978.

[26] Blazer *et al.*, Am. J. Clin. Path., 1983.

[27] Teele *et al.*, N. Eng. J. Med., 1981.

[28] *ibid.*

Appendix B

CASES OF BACTERIAL MENINGITIS ON FOLLOW-UP VISIT

Age (mo.)	6	8	8	24
Sex	F	F	M	M
Initial Visit:				
Temp (C)	38.9	41.1	39.3	41.1
White cell count	15500	6700	10000	9800
Blood Culture [1]	N.m.	N.m.	N.m.	N.m.
L.P.:	ND			
WBC		15	0	1
%PMN's		0	0	0
Culture [1]		NG	NG	NG
Diagnosis [2]	A	A	A	A
Therapy [3]	None	None	None	None
Time to F/U (days)	1	1	1	3
Follow-up visit:				
Temp (C)	38.0	39.6	38.0	38.5
White cell count	28500	11200	6700	9300
Blood Culture [1]	NG	NG	N.m.	N.m.
L.P.:				
WBC	2850	6300	3333	1660
%PMN's	87	85	94	72
Culture [1]	N.m.	N.m.	N.m.	N.m.
Diagnosis [2]	E	E	E	E
Therapy [3]	F	E	E	E

Age (mo.)	20	9	24	16
Sex	F	F	M	F
Initial Visit:				
Temp (C)	40.0	40.6	40.0	39.9
White cell count	22900	22700	8000	7200
Blood Culture [1]	H.i.	H.i.	H.i.	H.i.
L.P.:	ND		ND	ND
WBC		0		
%PMN's		0		
Culture [1]		NG		
Diagnosis [2]	A	G	B	A
Therapy [3]	B	None	B	None
Time to F/U (days)	1	2	1	1
Follow-up visit:				
Temp (C)	40.1	38.9	39.1	39.6
White cell count	16900	19700	15500	11200
Blood Culture [1]	H.i.	H.i.	NG	H.i.
L.P.:				
WBC	500	2044	1380	1900
%PMN's	81	94	90	91
Culture [1]	H.i.	NG	NG	H.i.
Diagnosis [2]	E	EH	E	E
Therapy [3]	F	F	F	F

Age (mo.)	19	11	7	22
Sex	F	F	F	M
Initial Visit:				
Temp (C)	40.8	41.0	39.7	39.7
White cell count	9900	16500	10900	17700
Blood Culture [1]	H.i.	S.p.	S.p.	S.p.
L.P.:			ND	
WBC	2	0		1
%PMN's	0	0		0
Culture [1]	NG	NG		NG
Diagnosis [2]	A	A	B	A
Therapy [3]	None	None	B	None
Time to F/U (days)	1	1	2	2
Follow-up visit:				
Temp (C)	39.7	39.0	38.9	41.1
White cell count	13300	2600	12700	17000
Blood Culture [1]	H.i.	S.p.	S.p.	S.p.
L.P.:				
WBC	7	500	494	3
%PMN's	100	95	75	80
Culture [1]	H.i.	S.p.	NG	S.p.
Diagnosis [2]	E	E	E	E
Therapy [3]	F	E	E	E

KEY:

[1]: NG- No growth
S.p.- *S. pneumoniae*
H.i.- *H. influenzae* type b
N.m.- *N. meningitidis*

[2]: A- Viral Syndrome/Fever
B- Otitis media
C- Pneumonia
D- Bacteremia
E- Bacterial meningitis
F- Aseptic meningitis
G- r/o sepsis
H- Bacterial sepsis
I- Leukemia

[3] A- p.o. Penicillin
B- p.o. Ampicillin/Amoxicillin
C- p.o. + i.m. Penicillin
D- p.o. + i.m. Ampicillin
E- i.v. Penicillin
F- i.v. Ampicillin or Ampicillin + Chloramphenicol

ND- Not Done

Appendix C

PRESENTATION OF PATIENTS WITH UNSUSPECTED BACTEREMIA BASED ON CAUSATIVE ORGANISM OF BACTEREMIA.

NOTES:

(1) Probabilities for continuous variables were determined using Fisher statistics, probabilities for categorical variables determined using Chi-square statistics. NS = Not Significant.

(2) There is a significant difference between temperature on initial visit for children with pnuemococcal and *H. influenzae* type b bacteremia ($P<0.005$ by t-test), but there is no significant difference in temperature on initial visit between children with *S. pneumoniae* or *H. influenzae* type b bacteremia, and *N. meningitidis* bacteremia.

(3) There is a significant difference in white blood cell counts at initial visit between children with pneumococcal and meningicoccal or *H. influenzae* type b bacteremia, but there is no significant difference in white blood counts between children with meningicoccal and *H. influenzae* type b bacteremia.

(4) Numbers in parentheses represent the total number of cases in which data about the clinical variable was present in the medical records.

	TYPE OF BACTERIA			
	S. pneumoniae	*H. influenzae* type b	*N. meningitidis*	Prob.(1)
GENERAL:				
Sex: M/F	75/64	18/22	3/4	N.S.
Mean Age(mo.)	23.2	27.8	45.7	N.S.
Mean Temp.(C) (4)	39.8(135)	39.4(39)	39.6(6)	<0.025 (2)
Mean WBC	18680(135)	15660(39)	12070(7)	<0.025 (3)
%PMN's	56.6(130)	55.3(35)	40.3(6)	N.S.
%Bands	15.5(130)	15.4(35)	25.7(6)	N.S.
Mean ESR	27.7(78)	33.3(23)	17.4(5)	N.S.
HISTORY:				
Median Duration of Symptoms (days)	2(139)	2(40)	1(7)	N.S.
T> 38.5 C	60(138)	11(39)	3(6)	N.S.
Activity abnormal	94(113)	30(34)	3(5)	N.S.
Feeding poorly	67(99)	18(28)	0(5)	<0.01
Stiff Neck	1(11)	1(1)	0(0)	N.S.
Seizure or poss. seizure	12(19)	3(4)	0(1)	N.S.
PHYSICAL EXAM:				
Appearance irrit., lethargic, "toxic"	87(130)	29(40)	5(6)	N.S.
Neck not supple	5(115)	1(36)	0(6)	N.S.
Ant. fontanelle full	1(34)	1(14)	1(3)	N.S.
DIAGNOSIS:				
Fever/URI	47	13	3	
Otitis media	50	9	0	
Pneumonia	14	8	0	
O.M.+Pneumonia	3	2	0	
R/O sepsis	5	1	3	
Aseptic meningitis	2	0	0	
Other	14	6	1	
Not noted	4	0	0	
TREATMENT:				
Antibiotics	77(139)	25(40)	0(7)	<0.01

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